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Race and Risk of Subsequent Aggressive Breast Cancer Following Ductal Carcinoma in Situ

Ying Liu, MD, PhD ^{1,2}; Robert West, MD³; Jason D. Weber, PhD^{2,4}; and Graham A. Colditz, MD, DrPH^{1,2}

BACKGROUND: General populations of black women have a higher risk of developing breast cancer negative for both estrogen receptor (ER) and progesterone receptor (PR) in comparison with white counterparts. Racial differences remain unknown in the risk of developing aggressive invasive breast cancer (IBC) that is characterized by negativity for both ER and PR (ER-PR-) or higher 21-gene recurrence scores after ductal carcinoma in situ (DCIS). **METHODS:** This study identified 163,892 women (10.5% black, 9.8% Asian, and 8.6% Hispanic) with incident DCIS between 1990 and 2015 from the Surveillance, Epidemiology, and End Results data sets. Cox proportional hazards regression was used to estimate hazards ratios (HRs) of subsequent IBC classified by the hormone receptor status and 21-gene recurrence scores. **RESULTS:** During a median follow-up of 90 months, 8333 women developed IBC. In comparison with white women, the adjusted HR of subsequent ER-PR- breast cancer was 1.86 (95% confidence interval [CI], 1.57-2.20) for black women (absolute 10-year difference, 2.2%) and 1.40 (95% CI, 1.14-1.71) for Asian women (absolute 10-year difference, 0.4%); this was stronger than the associations for ER+ and/or PR+ subtypes ($P_{\text{heterogeneity}} = .0004$). The 21-gene recurrence scores of subsequent early-stage, ER+ IBCs varied by race/ethnicity ($P_{\text{heterogeneity}} = .057$); black women were more likely than white women to have a recurrence score of 26 or higher (HR, 1.38; 95% CI, 1.00-1.92). No significant difference was observed in the risks of subsequent IBC subtypes for Hispanic women. **CONCLUSIONS:** Black and Asian women with DCIS had higher risks of developing biologically aggressive IBC than white counterparts. This should be considered in treatment decisions for black and Asian patients with DCIS. **Cancer** 2019;125:3225-3233. © 2019 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: breast cancer, ductal carcinoma in situ, race, recurrence.

INTRODUCTION

Ductal carcinoma in situ (DCIS), a nonobligate precursor to invasive breast cancer (IBC),¹ currently constitutes 20% to 30% of mammographically detected breast tumors.^{2,3} Approximately 64,000 new DCIS cases were expected to be diagnosed in the United States in 2018.² Although the 10-year survival rate is higher than 98%,⁴ more than 10% of patients with DCIS develop a second breast tumor within 10 years of their diagnosis, and half of these are invasive.³

We and others have demonstrated a significant variation by race and ethnicity in the risk of developing breast cancer after DCIS. Compared with white women, black women are more likely to have second tumors (invasive and noninvasive) in either breast and die of IBC after DCIS.⁵⁻¹¹ An increased risk of ipsilateral breast tumors has been observed in Hispanic women with DCIS,^{5,12} and an increased risk of contralateral breast tumors has been identified in Asian women with DCIS.⁵

In addition, our prior studies showed a higher proportion of estrogen receptor-positive (ER+) DCIS subtypes in black women than white women.^{5,6} However, black women with IBC who have no prior history of DCIS are far more likely than white counterparts to present with biologically aggressive features, including a lack of ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression and high RNA expression-based recurrence scores.¹³⁻¹⁵ It remains unknown whether black race (compared with white race) is associated with a higher risk of subsequently developing biologically aggressive breast cancer in patients with DCIS. In a large, racially diverse population of women with DCIS, we examined the risks of subsequent IBC subtypes, characterized by hormone receptor status and 21-gene recurrence scores, by race and ethnicity.

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MATERIALS AND METHODS

Patient Population

Women with unilateral DCIS diagnosed between January 1990 and June 2015 ($n = 211,439$) were identified from the 17 Surveillance, Epidemiology, and End Results (SEER) registries.¹² The Alaska Native Tumor Registry was excluded because of the small number of Alaskan Native patients. A data-use agreement form was required before access to the deidentified data set. Because the deidentified data were used, approval from the institutional review board of Washington University in St. Louis and patients' informed consent were not required.

We excluded patients with a prior cancer history ($n = 41,912$) and those younger than 20 years ($n = 19$). Approximately 97% of eligible cases were white, black, Asian (not including Pacific Islanders), or Hispanic; thus, women of other races or unknown race ($n = 5616$) were excluded if they were non-Hispanic. The final sample size was 163,892. In the analysis of ipsilateral breast cancer, we also excluded patients treated with mastectomy for DCIS and those whose surgical treatment was unknown ($n = 47,253$). Women treated with prophylactic mastectomy at initial DCIS ($n = 9638$) were also excluded from the analysis of contralateral breast cancer. Race and ethnicity were classified as non-Hispanic white (white), non-Hispanic black (black), non-Hispanic Asian (Asian), or Hispanic. Filipinos, Chinese, and Japanese were the 3 largest Asian subgroups and accounted for 63.4% of Asian patients. The majority of the Hispanics (95.5%) were white, and thus Hispanic whites and Hispanic non-whites were combined into a single group.

Covariates

Demographic factors included the age (20-39, 40-49, 50-59, 60-69, or 70-84 years) and year of DCIS diagnosis (1990-1999, 2000-2009, or 2010-2015) and registries. Histopathological features of DCIS included the tumor size (<2 cm, 2-5 cm, ≥ 5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), and histologic pattern (comedo, papillary, cribriform, solid, or not otherwise specified). Tumor size was also categorized with the cutoffs of 1 and 5 cm, and the results were similar (Supporting Table 1). Consistent with the literature,¹⁶ tumors were considered to be ER+ if the immunohistochemistry results of ER were positive or borderline. PR+ DCIS was similarly defined. Tumors positive for ER and/or PR were classified as hormone receptor-positive (ER+/PR+), and tumors negative for both ER and PR were classified as hormone receptor-negative (ER-PR-). Treatment for

DCIS was categorized as no surgical treatment, breast-conserving surgery alone, breast-conserving surgery plus radiation therapy, mastectomy, or unknown.

Outcomes

Subsequent breast cancer included IBC (reported to SEER registries) in either breast or metastatic breast cancer diagnosed at least 6 months after the initial DCIS. Ipsilateral IBCs were further classified as invasive recurrences arising in the same quadrant as the original DCIS and IBCs developing elsewhere in that same breast.¹⁷ Theoretically, the latter have the same incidence and characteristics as IBCs developing in the contralateral breast. Thus, IBCs arising in the ipsilateral breast away from the original DCIS and in the contralateral breast were combined. IBC subtypes were similarly defined by both ER and PR. For IBC cases diagnosed between 2004 and 2015, SEER data were linked to 21-gene recurrence score assay results from Genomic Health, Inc (Redwood City, California), by Information Management Services (Calverton, Maryland).¹⁸ IBC recurrence scores were categorized as low-risk (scores <18), intermediate-risk (scores = 18-30), or high-risk (scores ≥ 31).¹³⁻¹⁵ Because of the small number of racial minority patients who had 21-gene recurrence scores, we combined intermediate- and high-risk scores. A prospective trial (Trial Assigning Individualized Options for Treatment [TAILORx]) has demonstrated that chemotherapy does not benefit patients with early-stage, hormone receptor-positive IBC whose 21-gene recurrence scores are less than 26.¹⁹ We also dichotomized recurrence scores with a cutoff of 26.

Statistical Analysis

Baseline characteristics across racial/ethnic groups were compared with Pearson chi-square tests for categorical variables and with an analysis of variance for continuous variables. Cox proportional hazards regression was used to compute race-associated hazard ratios (HRs) and 95% confidence intervals (CIs) for subsequent IBC subtypes, and they were adjusted for the receptor status in the initial DCIS and the aforementioned covariates. Person-years were calculated from 6 months after the initial DCIS to the date of subsequent breast cancer, death, or December 31, 2015, whichever occurred first. A missing ER and PR status for subsequent IBC was considered for censoring. The assumption of proportionality for Cox models was confirmed with scaled Schoenfeld residuals. To determine whether race/ethnicity was differentially associated with IBC subtypes, an extension of the Cox proportional hazards regression models was used

to estimate the separate associations of race/ethnicity with the relative hazard of each subtype. Specifically, we used the approach proposed by Lunn and McNeil,^{20,21} in which each patient had a separate observation for each type of outcome and the analysis was stratified on outcome types. The initial full model assumed different associations of race/ethnicity and covariates with IBC subtypes. In a reduced model, race/ethnicity was constrained to have a single estimate across cancer subtypes, and the effects of covariates were allowed to be different. Likelihood ratio tests for heterogeneity were used to determine statistically significant differences in the associations of race/ethnicity with cancer subtypes. All statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, North Carolina). Statistical significance was assessed as a 2-sided P value $< .05$.

HER2 data were collected for breast cancers diagnosed after 2009. A secondary analysis was performed to compare the risks of subsequent IBC classified by ER, PR, and HER2. Subsequent breast cancers occurring before 2010 were analyzed as censoring.

RESULTS

Among 163,892 women with DCIS, 71.0% were non-Hispanic white, 10.5% were non-Hispanic black, 9.8% were non-Hispanic Asian, and 8.6% were Hispanic. Compared with white women, racial/ethnic minority women were younger at the initial DCIS and were more likely to have large, well-to-moderately differentiated, noncomedo lesions (each P value $< .0001$; Table 1). Black and Asian women underwent mastectomy more frequently than white and Hispanic women ($P < .0001$). The ER and PR status for the initial DCIS was available for 60.3% and 56.8% of cases, respectively. The frequency of ER–PR– DCIS was lower in the black group (11.4%) than other racial groups (white, 14.2%; Asian, 13.8%; Hispanic, 13.4%; $P < .0001$; Table 1).

During a median follow-up of 90 months, 8333 women developed IBC in either breast or metastatic breast cancer, and 7746 of these women (93.0%) had the ER and/or PR status available for their IBC. In comparison with white women, the overall risk of subsequent IBC was significantly increased in black women (HR, 1.42; 95% CI, 1.32-1.52; absolute 10-year risk difference, 2.2%; 95% CI, 1.7%-2.7%) but not in Asian women (HR, 1.08; 95% CI, 0.99-1.17; absolute 10-year risk difference, 0.4%; 95% CI, -0.1% to 0.8%) or Hispanic women (HR, 1.09; 95% CI, 1.00-1.18; absolute 10-year risk difference, 0.5%; 95% CI, 0%-1.0%). The associations were much stronger for ER–PR– subtypes than ER+/PR+ subtypes

($P_{\text{heterogeneity}} = .0004$; Table 2). In comparison with white women, the multivariable-adjusted HR of ER–PR– IBC was 1.86 (95% CI, 1.57-2.20) in black women, 1.40 (95% CI, 1.14-1.71) in Asian women, and 1.24 (95% CI, 1.00-1.54) in Hispanic women. Black women also had a significantly higher risk of subsequent triple-negative (negative for ER, PR, and HER2) breast cancer (HR, 1.99; 95% CI, 1.44-2.75), and Asian women had a significantly higher risk of subsequent HER2+ breast cancer (HR, 1.85; 95% CI, 1.21-2.84; Supporting Table 2).

We further examined the risks separately for ipsilateral and contralateral IBC by race/ethnicity (Table 2). In comparison with white women, the risk of ipsilateral IBC was significantly higher in black (HR, 1.65; 95% CI, 1.49-1.83; absolute 10-year risk difference, 2.1%; 95% CI, 1.6%-2.6%), Asian (HR, 1.23; 95% CI, 1.09-1.38; absolute 10-year risk difference, 0.7%; 95% CI, 0.3%-1.2%), and Hispanic women (HR, 1.19; 95% CI, 1.05-1.35; absolute 10-year risk difference, 0.6%; 95% CI, 0.2%-1.1%). There was no significant heterogeneity in the associations for risks of ipsilateral cancer subtypes ($P_{\text{heterogeneity}} = .57$; Table 2). The multivariable-adjusted HR for ipsilateral ER–PR– subtypes was 1.83 (95% CI, 1.43-2.35) in black women, 1.34 (95% CI, 0.99-1.81) in Asian women, and 1.40 (95% CI, 1.05-1.87) in Hispanic women.

In comparison with white women, the risk of contralateral IBC was significantly increased in black women (HR, 1.18; 95% CI, 1.07-1.31; absolute 10-year risk difference, 0.6%; 95% CI, 0.2%-0.9%). This association was much stronger for ER–PR– subtypes (HR, 1.97; 95% CI, 1.55-2.52) than ER+/PR+ subtypes (HR, 1.07; 95% CI, 0.95-1.20; $P_{\text{heterogeneity}} < .0001$). Although the risk of overall contralateral IBC was similar between Asian and white women (HR, 0.97; 95% CI, 0.86-1.10; absolute 10-year risk difference, 0.1%; 95% CI, -0.4% to 0.3%), Asian women had a significantly higher risk of ER–PR– subtypes (HR, 1.61; 95% CI, 1.20-2.16). The risks of overall contralateral breast cancer and subtypes were all comparable between Hispanic and white women.

Subsequent breast cancers were also categorized on the basis of both the laterality and locations of the original DCIS and subsequent IBC (Table 3). Among 3010 cases with known locations for both the original DCIS and subsequent ipsilateral IBC, 21.4% developed IBC in the same quadrant of the same breast as the original DCIS. Compared with white women, black women had significantly higher risks of developing IBC in the same quadrant of the same breast as the original DCIS (HR, 1.51; 95% CI, 1.18-1.93; absolute 10-year risk difference, 0.3%; 95% CI, 0.1%-0.5%) and IBC in the

TABLE 1. Age and Age-Standardized Characteristics of Women With Unilateral DCIS in SEER by Race and Ethnicity (n = 163,892), 1990-2015

	White	Black	Asian	Hispanic	<i>P</i> ^a
No. of cases	116,431	17,274	16,039	14,148	
Age, mean (SD), y	59.5 (12.4)	58.3 (12.2)	56.4 (11.7)	56.2 (11.8)	<.0001
Age at diagnosis, %					
20-39 y	3.1	4.4	4.5	4.8	
40-49 y	20.9	21.5	27.5	28.1	
50-59 y	27.8	29.2	30.0	29.9	
60-69 y	24.9	25.5	22.8	21.9	
≥70 y	23.3	19.5	15.2	15.3	<.0001
Length of follow-up, median (range), mo	95 (6-311)	79 (6-311)	83 (6-311)	75 (6-311)	<.0001
Length of follow-up, %					
6-11 mo	3.3	4.8	5.0	5.9	
12-59 mo	27.0	33.8	32.0	35.1	
60-119 mo	31.3	32.5	30.9	31.9	
≥120 mo	38.4	28.8	32.1	27.2	<.0001
Year of first DCIS diagnosis, %					
1990-1999	17.0	12.7	14.3	10.1	
2000-2009	53.3	49.9	48.3	49.3	
2010-2015	29.7	37.4	37.5	40.6	<.0001
Histologic subtype, %					
Not otherwise specified	66.9	68.4	67.5	68.3	
Comedo	13.5	11.4	11.8	11.6	
Papillary	5.2	7.0	5.0	5.4	
Cribriform	8.5	8.2	10.0	9.4	
Solid	5.9	5.0	5.8	5.3	<.0001
Grade, %					
Well differentiated	13.7	16.6	14.1	14.3	
Moderately differentiated	40.0	43.3	43.3	43.6	
Poorly differentiated	46.3	40.1	42.6	42.1	<.0001
Tumor size, %					
<2.0 cm	75.3	69.9	69.2	70.0	
2.0-4.9 cm	19.2	21.8	24.9	22.8	
≥5.0 cm	5.5	8.3	5.9	7.2	<.0001
ER, %					
Negative	15.9	12.9	15.5	14.9	
Positive	84.1	87.1	84.5	85.1	<.0001
PR, %					
Negative	26.1	21.9	23.9	24.7	
Positive	73.9	78.1	76.1	75.3	<.0001
Hormone receptor status, %					
ER- and PR-	14.2	11.4	13.8	13.4	
ER+ or PR+	85.8	88.6	86.2	86.6	<.0001
Treatment for primary DCIS, %					
No surgery	2.2	3.4	2.1	3.0	
BCS alone	24.7	23.4	23.0	26.2	
BCS and radiation	44.3	43.6	44.0	43.7	
Mastectomy	28.9	29.5	31.0	27.1	<.0001

Abbreviations: BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.

Race and ethnicity were classified into mutually exclusive categories: non-Hispanic white (hereafter called white), non-Hispanic Black (black), non-Hispanic Asian (Asian), and Hispanic (Hispanic). Supporting Table 6 shows distributions of missing values for each variable across race groups. Due to rounding, percentages did not always add up to 100%.

^a*P* values were calculated from comparisons across all groups except for groups with missing values.

ipsilateral breast away from the original DCIS and in the contralateral breast (HR, 1.34; 95% CI, 1.24-1.45; absolute 10-year risk difference, 1.5%; 95% CI, 1.1%-2.0%). The increased risk of IBC in the ipsilateral breast away from the original DCIS and in the contralateral breast was much stronger for ER-PR- subtypes (HR, 1.93; 95% CI, 1.60-2.40) than ER+/PR+ subtypes (HR for ER+/PR+, 1.24; 95% CI, 1.13-1.36)

in black women ($P_{\text{heterogeneity}} < .0001$). In comparison with white women, the risk was significantly increased for ER-PR- IBC developing in the ipsilateral breast away from the original DCIS and in the contralateral breast in Asian women (HR, 1.45; 95% CI, 1.15-1.82) but not for ER+/PR+ subtypes (HR, 0.99; 95% CI, 0.89-1.10). There was no significant difference in the risk of developing IBC in the same quadrant of the

TABLE 2. Adjusted HRs of Subsequent IBC Classified by Laterality and Hormone Receptor Status According to Race and Ethnicity in Women With DCIS in SEER, 1990-2015

		All Second Invasive Events ^a			ER+ or PR+		ER– and PR–	
		Person-y	Cases, No.	HR ^b (95% CI)	Cases, No.	HR ^b (95% CI)	Cases, No.	HR ^b (95% CI)
Subsequent IBC ^c	White	1,018,475	5884	1.00	4653	1.00	821	1.00
	Black	129,931	1002	1.42 (1.32-1.52)	720	1.31 (1.21-1.43)	190	1.86 (1.57-2.20)
	Asian	128,657	807	1.08 (0.99-1.17)	620	1.01 (0.92-1.11)	135	1.40 (1.14-1.71)
	Hispanic	102,614	640	1.09 (1.00-1.18)	505	1.09 (0.99-1.20)	102	1.24 (1.00-1.54)
								$P_{\text{heterogeneity}} = .0004$
Ipsilateral IBC ^d	White	709,275	2438	1.00	1846	1.00	393	1.00
	Black	89,081	478	1.65 (1.49-1.83)	341	1.58 (1.40-1.78)	86	1.83 (1.43-2.35)
	Asian	86,294	378	1.23 (1.09-1.38)	286	1.19 (1.03-1.36)	61	1.34 (0.99-1.81)
	Hispanic	72,785	309	1.19 (1.05-1.35)	235	1.20 (1.04-1.38)	59	1.40 (1.05-1.87)
								$P_{\text{heterogeneity}} = .57$
Contralateral IBC ^e	White	971,003	3134	1.00	2556	1.00	363	1.00
	Black	126,291	446	1.18 (1.07-1.31)	322	1.07 (0.95-1.20)	92	1.97 (1.55-2.52)
	Asian	125,104	396	0.97 (0.86-1.10)	306	0.89 (0.78-1.02)	68	1.61 (1.20-2.16)
	Hispanic	98,900	292	0.98 (0.87-1.11)	234	0.97 (0.84-1.11)	38	1.13 (0.80-1.60)
								$P_{\text{heterogeneity}} < .0001$

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; ER, estrogen receptor; IBC, invasive breast cancer; HR, hazard ratio; PR, progesterone receptor; SEER, Surveillance, Epidemiology, and End Results.

^aSecond IBCs included those positive for ER or PR (ER+ or PR+), those negative for both ER and PR (ER–PR–), and those with no information on ER and PR.

^bHRs were adjusted for the following: age (20-39, 40-49, 50-59, 60-69, or ≥70 years) and year of the primary DCIS diagnosis (1990-1999, 2000-2009, or 2010-2015); registry; treatment for primary DCIS (no surgical treatment, breast-conserving surgery alone, breast-conserving surgery followed by radiation therapy, mastectomy, or unknown); and histopathological features of primary DCIS, including the tumor size (<2 cm, 2-5 cm, ≥5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), histology (comedo, papillary, cribriform, solid, or not otherwise specified), and hormone receptor expression (positive, negative, or unknown).

^cSubsequent IBCs included ipsilateral IBCs, contralateral IBCs, and subsequent metastatic breast cancers.

^dThe analysis included the patients who had been treated with breast-conserving surgery or no surgical treatment for their primary DCIS.

^ePatients who had undergone bilateral mastectomy for their primary DCIS were excluded.

TABLE 3. Adjusted HRs of Developing IBC in the Same Quadrant of the Same Breast as the Original DCIS and IBC in the Ipsilateral Breast Away From the Original DCIS or the Contralateral Breast According to Race and Ethnicity in Women With DCIS in SEER, 1990-2015

		All Second Invasive Events ^a			ER+ or PR+		ER– and PR–	
		Person-y	Cases, No.	HR ^b (95% CI)	Cases, No.	HR ^b (95% CI)	Cases, No.	HR ^b (95% CI)
IBC in ipsilateral breast away from original DCIS and in contralateral breast	White	971,003	4741	1.00	3776	1.00	630	1.00
	Black	126,291	755	1.34 (1.24-1.45)	547	1.24 (1.13-1.36)	149	1.93 (1.60-2.40)
	Asian	125,104	648	1.06 (0.97-1.17)	497	0.99 (0.89-1.10)	107	1.45 (1.15-1.82)
	Hispanic	98,900	489	1.05 (0.95-1.16)	388	1.05 (0.94-1.17)	71	1.14 (0.88-1.47)
								$P_{\text{heterogeneity}} < .0001$
IBC in same quadrant of same breast as original DCIS	White	709,275	431	1.00	327	1.00	62	1.00
	Black	89,081	83	1.51 (1.18-1.93)	63	1.47 (1.10-1.95)	11	1.48 (0.75-2.90)
	Asian	86,294	71	1.15 (0.87-1.52)	55	1.16 (0.84-1.59)	13	1.49 (0.75-2.98)
	Hispanic	72,785	60	1.16 (0.88-1.54)	47	1.22 (0.89-1.67)	12	1.63 (0.85-3.13)
								$P_{\text{heterogeneity}} = .80$

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HR, hazard ratio; IBC, invasive breast cancer; PR, progesterone receptor; SEER, Surveillance, Epidemiology, and End Results.

^aSecond IBCs included those positive for ER or PR (ER+ or PR+), those negative for both ER and PR (ER–PR–), and those with no information on ER and PR.

^bHazard ratios were adjusted for the following: age (20-39, 40-49, 50-59, 60-69, or ≥70 years) and year of the primary DCIS diagnosis (1990-1999, 2000-2009, or 2010-2015); registry; treatment for primary DCIS (no surgical treatment, breast-conserving surgery alone, breast-conserving surgery followed by radiation therapy, mastectomy, or unknown); and histopathological features of primary DCIS, including the tumor size (<2 cm, 2-5 cm, ≥5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), histology (comedo, papillary, cribriform, solid, or not otherwise specified), and hormone receptor expression (positive, negative, or unknown).

same breast as the original DCIS, in a different quadrant of the same breast, or in the contralateral breast between Hispanic and white women.

Among 5045 patients with DCIS who subsequently developed early-stage (I, II, or IIIa), ER+ IBC between 2004 and 2015, 1184 (23.5%) had 21-gene

TABLE 4. Multivariable-Adjusted HRs for Higher Levels of 21-Gene Recurrence Scores for Early-Stage, Hormone Receptor-Positive Invasive Breast Cancer Among Women With DCIS in SEER, 1990-2015

	Person-y	Recurrence Scores							
		<18		≥18		<26		≥26	
		Cases, No.	HR ^a (95% CI)	Cases, No.	HR ^a (95% CI)	Cases, No.	HR ^a (95% CI)	Cases, No.	HR ^a (95% CI)
White	1,018,475	421	1.00	421	1.00	602	1.00	240	1.00
Black	129,931	58	1.11 (0.84-1.46)	68	1.29 (1.00-1.67)	84	1.13 (0.90-1.42)	42	1.38 (1.00-1.92)
Asian	128,657	77	1.37 (1.07-1.75)	57	0.97 (0.73-1.28)	97	1.19 (0.96-1.48)	37	1.11 (0.78-1.57)
Hispanic	102,614	50	1.17 (0.87-1.57)	32	0.71 (0.50-1.02)	64	1.03 (0.80-1.34)	18	0.71 (0.44-1.14)
<i>P</i> _{heterogeneity} = .046					<i>P</i> _{heterogeneity} = .057				

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.

^aHazard ratios were adjusted for the following: age (20-39, 40-49, 50-59, 60-69, or ≥70 years) and year of the primary DCIS diagnosis (1990-1999, 2000-2009, or 2010-2015); treatment for primary DCIS (no surgical treatment, breast-conserving surgery alone, breast-conserving surgery followed by radiation therapy, mastectomy, or unknown); and histopathological features of primary DCIS, including the tumor size (<2 cm, 2-5 cm, ≥5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), histology (comedo, papillary, cribriform, solid, or not otherwise specified), and hormone receptor expression (positive, negative, or unknown).

recurrence scores. There was no significant racial difference in the use of 21-gene assays (Supporting Table 3). Recurrence scores varied by race/ethnicity (*P*_{heterogeneity} = .046-.057; Table 4). In comparison with white women, the risk of subsequent ER+ IBC with a recurrence score of 26 or higher was increased in black women (HR, 1.38; 95% CI, 1.00-1.92). Using the developed cutoffs for intermediate and high recurrence risk, we observed a similar result for black women (HR, 1.29; 95% CI, 1.00-1.67). There was no significant difference in Asian and Hispanic women in comparison with white women in the risk of developing aggressive ER+ IBC defined by recurrence scores.

DISCUSSION

Our prior analysis of the 1990-2009 SEER data demonstrated a significantly higher risk of subsequently developing IBC in black women with DCIS than white counterparts.⁵ Using immunohistochemically assessed tissue markers and 21-gene recurrence scores, the current study extends this finding to biologically aggressive IBC in a population-based, racially diverse group of patients with DCIS. Compared with white women, black women had a higher risk of developing IBC characterized by ER-PR- subtypes and higher recurrence scores in ER+ tumors after DCIS. This is consistent with the higher risk of developing ER-PR- IBC in the general population of black women.^{13,22,23} Asian women were more likely than white women to develop ER-PR- IBC. To our knowledge, this is the only study to date examining racial differences in subsequent IBC subtypes after DCIS.

Our finding of a higher risk of developing aggressive breast cancer in black women with DCIS in comparison

with white counterparts may have clinical relevance. Black women with DCIS are more likely than white counterparts to die of breast cancer.¹¹ In the setting of IBC, basal-like tumors disproportionately affect African American women.^{13,22,23} Basal-like tumors overlap largely with triple-negative tumors, which have a poor prognosis. Most ER-PR- breast cancers (73%) are negative for HER2.¹⁶ We observed that the risk of triple-negative breast cancer was nearly doubled after DCIS in black women compared with white women. Therefore, a higher risk of developing ER-PR- IBC in black women with DCIS may contribute to their worse survival.

Two distinct types of ipsilateral breast cancer recurrence have been proposed: true local recurrences and new ipsilateral primary tumors.^{17,24,25} They are generally distinguished from each other on the basis of both histopathology and location.^{17,26,27} True recurrences have a histopathology similar to that of primary tumors and are close to the primary tumor bed. True recurrences may reflect regrowth of clonogenic cells that have not been completely removed by local treatment. New primary IBCs are independent of the original breast cancer and have different clinical features and a different prognosis than true recurrences.^{17,26,27} The development of new primary IBC has been considered a result of a genetic predisposition to breast cancer and is associated with higher occurrences of contralateral IBC.²⁸ We observed that the risk of developing IBC in the ipsilateral breast away from the original DCIS and contralateral breasts, particularly hormone receptor-negative subtypes, was significantly increased in black women. This indicates an underlying genetic susceptibility to breast cancer, early-life behavioral exposures, and/or their interactions

in black women. Prior studies demonstrated that patients with true local recurrence had worse survival than those with new ipsilateral primary IBC.^{26,27} Our finding of a higher risk of developing ipsilateral IBC in the same quadrant of the breast in black patients may contribute to their worse survival. Molecular assays (eg, a loss of heterozygosity) are more reliable approaches for showing clonal relationships between original tumors and ipsilateral IBCs and for distinguishing genetically related recurrences from genetically distinct new primaries.^{24,25} Racial differences in the distinct types of ipsilateral IBC need to be confirmed with molecular methods.

The 21-gene recurrence score is an assay based on reverse transcription–polymerase chain reaction that is currently applied to early-stage, ER+ IBC to assess the prognosis and the likely benefit from chemotherapy in addition to endocrine therapy.²⁹ Using the TAILORx-defined cutoff value of 26,¹⁹ we observed that black patients with DCIS were more likely than white counterparts to subsequently develop aggressive ER+ IBC. Using commonly used definitions of intermediate (18–30) and high recurrence risks (≥ 31) generated a similar result. This finding was consistent with the racial difference in RNA expression–based recurrence scores reported for first primary IBC.^{13–15} A recent analysis of TAILORx trial data (including 8189 whites, 693 blacks, 405 Asians, and 432 others) showed a similar distribution of recurrence scores across race groups in patients with early-stage, hormone receptor–positive, HER2– IBC (with no prior diagnosis of DCIS) and worse survival for black patients.³⁰ Our finding needs to be confirmed in future studies with a larger number of black patients with DCIS who have 21-gene assay results for subsequent IBC.

Biological differences (other than intrinsic subtypes) between IBC in black women and white women have been identified. In a comprehensive analysis of genomic, transcriptomic, and proteomic data from the Cancer Genome Atlas, Huo et al³¹ found that a number of molecular features differed between black and white IBCs after adjustments for age and subtypes, including the DNA copy number, gene expression, and DNA methylation. Gene expression profiling of luminal A and basal-like IBCs identified 6 genes that were differentially expressed between black and white patients and were also associated with survival.³² In that study, some poor outcome–associated genes were upregulated in cancer-adjacent normal breast tissue from black women versus white women. Our data are consistent with the idea that black women exhibit genetic profiles in nascent tumor cells and/or surrounding normal cells that create a race-associated biological difference.

This race-associated genetic difference may occur at the earliest stages of carcinogenesis.

We observed a higher risk of developing ER–PR– IBC in Asian women with DCIS than white counterparts. The clinical relevance of this finding remains to be determined because there were no survival differences between Asians and whites among patients with DCIS from SEER.¹¹ Within Asian American women with their first primary IBC, distributions of ER–PR– subtypes have been reported to vary across ethnic groups, with the highest frequency in South Asians and the lowest frequency in Japanese and Chinese.^{33,34} The number of Asian patients with DCIS with subsequent IBC did not allow us to examine ethnic differences among Asian women.

This study has limitations. Some variables influencing DCIS outcomes (eg, surgical margins and endocrine therapy) were unavailable. Prior studies reported no racial differences in surgical margins or endocrine therapy in patients with DCIS.^{6,9,35,36} Among those who initiated endocrine therapy, blacks were more likely than whites to be nonadherent to therapy, and Asians were more likely to continue therapy.³⁷ Obesity and alcohol consumption have been associated with an increased risk of subsequent breast cancer in patients with DCIS.^{38,39} We were unable to assess their contributions to racial differences in DCIS outcomes. The duration of follow-up was longer in white patients than racial minority patients. However, the exclusion of patients diagnosed after 2010 did not significantly change the race-associated risks (Supporting Table 4). Approximately 40% of DCIS cases had no hormone receptor data, and missing indicators were used in the analysis. This approach has been demonstrated to have no significant impacts on the estimated associations between exposures and cancer outcomes when missingness is less than 50%.⁴⁰ The finding of a race-associated higher risk of ER–PR– IBC in all eligible patients was consistent with a race-associated higher risk of the hormone receptor status changing from positive to negative observed in a subgroup of patients who had complete hormone receptor data for both DCIS and subsequent IBC (Supporting Table 5). The 21-gene recurrence scores were available for only 24% of patients with DCIS who subsequently developed early-stage, ER+ IBC. Among women with IBC who had no history of DCIS, black race has been associated with underutilization of 21-gene assays and higher recurrence scores.^{14,15} Therefore, a higher risk of recurrence score–defined aggressive IBC in black women with DCIS may reflect racial differences in testing. However, there was no significant racial difference in 21-gene testing in our sample.

Overall, we provide evidence for a higher risk of subsequently developing aggressive IBC in black and Asian patients with DCIS in comparison with white counterparts. This gives us a better understanding of racial influences on the risk of IBC after the diagnosis of DCIS and should be considered in the management of DCIS. Although the molecular and genetic features underlying this higher risk remain undiscovered, we have now specified the biological context for studying these inherent racial differences. Future work will assess its contribution to poorer survival in black women with DCIS. A better understanding of race-associated biological and nonbiological differences in the progression of DCIS will help to distinguish high-risk patients with DCIS from low-risk patients with DCIS and improve personalized treatment to reduce the disproportionate burden of breast cancer in black women.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Ying Liu: Full access to all the data in the study and responsibility for the integrity of the data and the accuracy of the data analysis; concept and design; statistical analysis; drafting of the manuscript; acquisition of funding; administrative, technical, or material support; supervision; acquisition, analysis, or interpretation of data; and critical revision of the manuscript for important intellectual content. **Robert West:** Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. **Jason D. Weber:** Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. **Graham A. Colditz:** Concept and design; acquisition of funding; administrative, technical, or material support; supervision; acquisition, analysis, or interpretation of data; and critical revision of the manuscript for important intellectual content.

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